

## **REMARKS**

### **Status of the Claims**

Claims 6, 7, 12, 13, and 15-23 have been withdrawn. Claims 1-5, 8-11, 14, and 24-34 were pending and examined in the September 12, 2006 Office Action. In this reply, claims 25-28 have been cancelled, and claims 24 and 32 amended. No new matter has been added. Accordingly, claims 1-5, 8-11, 14, 24, and 29-34 will be pending upon entry of this amendment.

Claim 24 has been amended to claim with more particularity the site of desired tissue growth. Support for this amendment is found in the original application at page 7, lines 23-26 and original claims 25-28. Claim 24 has also been amended to more particularly claim the complexed-acidic-phospholipid-collagen composite as comprising calcium, phospholipids, inorganic phosphate, and collagen. Support for this amendment is found in the original application at page 4, lines 25-27, page 8, lines 16-17, and original claim 1.

Claim 32 has been amended to clarify the term "nanomaterials." Support for this amendment is found in the original application at page 13, line 6.

### **Information Disclosure Statement**

The Examiner states that the Information Disclosure Statement submitted November 12, 1004 fails to comply with 37 CFR 1.98(a)(1) with respect to the "International Search Report dated 07-26-2004". It is respectfully submitted that the only patent listed in the International Search Report is U.S. 6,311,690, which is separately listed under U.S. Patent Documents on the Form PTO-1449 accompanying the November 12, 2004 Information Disclosure Statement (see Cite AA on Form PTO-1449). Thus, the November 12, 2004 Information Disclosure Statement meets the requirements of 37 CFR 1.98(a)(1) and should be considered.

**Rejections under 35 U.S.C § 112, Second Paragraph**

Independent claim 24, and claims 25-34 which depend therefrom, are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner contends that the term “at a site in need of desired tissue growth” is vague and unclear. Claim 24 has been amended to include the specific examples of sites in need of desired tissue growth including bone, calcifying cartilage, dentin, and cementum. Because the amendment to claim 1 incorporates the limitations of dependent claims 25-28, these claims have been cancelled.

Claim 32 also is rejected under 35 U.S.C. § 112, second paragraph, as indefinite, as to the use of the term “nanomaterials.” Claim 32 has been amended to delete this term and use the terms carbon fibers and nanotubes, specific examples of nanomaterials set forth in the specification at page 15, line 6.

It is respectfully submitted that claims 24 and 29-34 as amended are clear and meet the requirements of 35 U.S.C. § 112, second paragraph.

**Rejections under 35 U.S.C. § 102(a)**

Claims 24, 25, 29, 30 and 32 are rejected under 35 U.S.C. § 102(a) as being anticipated by U.S. Patent No. 6,311,690 issued to Jefferies (“Jefferies”). The Examiner contends that the claims cover a method of inducing the growth of bone in a mammal comprising administering complexed-acidic-phospholipid-collagen composite at the site in need of desired tissue growth. The Examiner further contends that Jefferies teaches a reconstituted collagen and acidic-phospholipids conjugate composition that is useful in promoting bone growth as covered in claims 24 and 25. Additionally, the Examiner asserts that Jefferies discloses the composition being administered as an implant as covered in claim 29, being prepared in an organic polymer as covered in claim 30, and comprising the further materials as covered in claim 32. *See* Office Action dated September 12, 2006, page 4.

While Jefferies does disclose a method for inducing bone growth comprising collagen and demineralized bone particles, and suggests that the collagen matrix can be strengthened with acidic phospholipids, as acknowledged by the Examiner, Jefferies does not teach or suggest a complexed-acidic-phospholipid-collagen complex comprising calcium, phospholipids, inorganic phosphate, and collagen as called for in the present claims. Independent claim 24 has been amended to cover a method wherein the complexed-acidic-phospholipid-collagen composite comprising calcium, phospholipid, inorganic phosphate, and collagen, is used for inducing bone growth. Claims 25, 29, 30, and 32 depend from claim 24 and now also contain this limitation. Thus, claims 24, 25, 29, 30, and 32 as amended are not anticipated by Jefferies because this specific limitation of a complex comprising calcium, phospholipid, inorganic phosphate, and collagen is missing from the reference.

**Rejections under 35 U.S.C. § 102(b)**

Claims 1-5 and 8-11 are rejected as being anticipated by Boskey, The Journal of Physical Chemistry (1989) 93:1628 ("Boskey"). The Examiner contends that Boskey's teaching of a dynamic collagen system comprising synthetic complexed acidic phospholipids comprising calcium chloride, phosphatidylserine, and ammonium phosphate reads on claims 1-5 and 8-11. See Office Action dated September 12, 2006, page 5. This rejection is respectfully traversed.

Boskey discloses a dynamic hydroxyapatite growth formation system wherein calcium and phosphate solutions are pumped over gels made of gelatin. Boskey, page 1628-29. Other macromolecules were added to the gels, including complexed acidic phospholipids, proteoglycans, and rat tail collagen. Boskey, page 1629-30. This is not the composition defined in the present claims.

The Boskey article does not disclose a composition wherein all of the components of the claimed composition are present. The gel in the Boskey reference is made of gelatin. Gelatin is water-soluble jelly-like protein product produced by the partial hydrolysis of collagen. Because gelatin is denatured collagen, the natural molecular bonds between the individual collagen strands are broken down into a structural form that rearranges more easily. Gelatin has the distinguishing property of

melting when heated, and solidifying when cooled again. It is used, for example, as a food additive, a pill coating, a base for ointments, and a biological substrate for cell culture. See Columbia Electronic Encyclopedia definition of “gelatin”, found in Reference.com, attached at Tab 1. See also Collins Dictionary of Biology, attached at Tab 2, page 279.

In contrast, collagen is the main protein of connective tissue in animals. Collagen is a long, fibrous structural protein and is the major component of connective tissue. Collagen consists of white inelastic fibers which include fine fibrils, which are composed of ever finer filaments, visible only with an electron microscope. Collagen molecules consist of three polypeptide chains coiled around each other to form a triple helix, stabilized by hydrogen bonds. Collagen is used for cosmetic surgery and treatment of burns. See Columbia Electronic Encyclopedia definition of “collagen”, found in Reference.com, attached at Tab 3. See also Tab 2, page 163.

Collagen and gelatin are not the same material: gelatin is a denatured form of collagen and lacks its fundamental properties. Not only do they have very different structures, they also have very different uses. Collagen is a protein found in its natural state in the form of helices, with great tensile strength. Due to this structure, collagen could not be used as a food additive or as an additive in pharmaceutical capsules. Gelatin, which is a protein product, is well-suited for these uses because of its lack of helices and tensile strength, and its jelly-like structure. These two substances are not identical, and not even interchangeable, as they have such different structures and functions. In order to anticipate, a reference must disclose the identical limitation, not an equivalent or nearly identical one. *Richardson v. Suzuki Motor Co. Ltd*, 868 F.2d 1226, 1236 (Fed. Cir. 1989), *cert. denied*, 493 U.S. 853 (1989).

Moreover, while rat skin collagen fibers are added to the system in Boskey, they are never *added in combination* with the complexed acidic phospholipids. Boskey, page 1631. Thus, Boskey does not disclose or suggest the currently claimed complex comprising a complexed acidic phospholipid, and collagen.

Thus, Boskey does not anticipate claims 1-5 and 8-11 because it does not teach or suggest every claim limitation. Specifically, the limitation of a composite material for osteoinduction comprising an acidic-phospholipid complex and *collagen* is missing in Boskey. Claims 2-5 and 8-11 depend from claim 1 and contain every limitation of claim 1. Thus, Boskey does not anticipate these claims as well.

Claims 2-5 and 8-11 are also novel over Boskey for additional reasons. These claims cover complexes with specific ratios of calcium, phospholipid, and inorganic phosphate (claims 2-4), or complexes specifically containing calcium chloride (claim 5), phosphatidylserine (claims 8-9), or ammonium acid phosphate (claims 10-11). The Examiner argues that Boskey teaches a dynamic collagen gel system comprising synthetic complexed acidic phospholipids (calcium-phospholipid-phosphate complex comprising  $\text{CaCl}_2$ ,  $(\text{NH}_4)_2\text{HPO}_4$  and phospholipids in a molar ratio of 50% Ca, 40% phospholipids and 10% inorganic  $\text{PO}_4$ ). In support of this contention, the Examiner relies upon an earlier 1977 Boskey paper. It is respectfully submitted that the 1977 Boskey paper is not cited anywhere within Boskey, let alone in the section discussing the complexed acidic phospholipids. It is impossible from Boskey alone to ascertain the specific components, or the ratio of components, in the complex.

Thus, for these reasons, claim 1-5 and 8-11 are not anticipated by Boskey, and this rejection should be withdrawn.

### **Rejections under 35 U.S.C. § 103**

The Examiner contends that claims 27-28<sup>1</sup> and 31 are obvious over Jefferies in view of U.S. Patent No. 4,578,384 issued to Hollinger ("Hollinger"). Hollinger is being used by the Examiner as a supplemental reference to demonstrate the use of biocompatible copolymer such as polyglycolic acid and polyactic acid in combination with acidic phospholipid complex for improving and promoting the healing of osseous tissue including bone, cementum and dentin. The Examiner

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<sup>1</sup> These claims have been cancelled in this amendment. However, the specific limitations covered in these claims have been added by amendment to claim 24. Thus, the arguments as to these claims being unobvious are still relevant.

contends that the use of a biocompatible copolymer as a secondary agent for preparing the acidic phospholipids as set forth in claim 31 and the use of the acidic complex composition in healing osseous tissues such as dentin and cementum as set forth by claims 27 and 28 would have been obvious by combining the teachings of Jefferies with Hollinger. This rejection is respectfully traversed.

In order to establish *prima facie* obviousness, the Examiner must show: (1) the references alone or in combination teach or suggest all of the claim limitations; (2) some suggestion and/or motivation in the references or the general knowledge of the art to modify or combine the references; and (3) a reasonable expectation of success. Here, the Examiner has not established any of these three criteria.

In view of the amendment to independent claim 24, Jefferies does not teach or suggest all of the limitations of that claim, which are also found in dependent claims 27-28 and 31. As discussed above, Jefferies does not teach or suggest a complexed-acidic-phospholipid-collagen complex comprising calcium, phospholipids, inorganic phosphate, and collagen. The secondary reference, Hollinger, does not disclose or suggest this missing limitation. Thus, the references either alone or in combination do not teach or suggest all of the claim limitations.

Furthermore, there would have been no motivation to combine the teachings of these two references because Hollinger teaches away from Jefferies. Jefferies teaches the use of collagen and demineralized bone particles for bone repair. Hollinger teaches a material consisting of a combination of proteolipid and biodegradable, biocompatible copolymer for the healing of osseous tissue. Hollinger further discloses that this “represents a significant improvement over conventional materials” such as collagen and bone derivatives, the materials used in Jefferies. See Hollinger, column 2, lines 38-50. One of the disadvantages of these materials, according to Hollinger, is an unwanted immunologic response. *Id.* at column 4, lines 12-20. In view of this teaching in Hollinger, there would have been no motivation to combine the teachings of these two references as this patent teaches away from Jefferies because Jefferies uses the materials, *e.g.*, collagen and bone particles, that promote unwanted immune responses, and over which Hollinger “represents a

significant improvement.” *See In re Lundsford*, 148 U.S.P.Q. 721, 726 (CCPA 1966). Given that Hollinger states that the materials used in Jefferies would be undesirable and likely cause an unwanted immune reaction, one of skill in the art would not look to combine the teachings of the two references as Hollinger suggests that the result of combining the two would not achieve a desirable result. *See Tec Air Inc. v. Denos Mfg. Mich., Inc.*, 192 F.3d 1353, 1360 (Fed. Cir. 1998). Indeed, the Examiner’s own citation in support of his assertion actually teaches away from combining the material disclosed in Hollinger with the material disclosed in Jefferies. *See* Office Action dated September 12, 2006, page 7; Hollinger, column 14, lines 28-32 (“The results of applicant’s evaluation indicate that copolymer-proteolipid implant material was very successful at stimulating the early phases of bone repair and that it can be used *as an unexpectedly superior alternative to the agents commonly employed for bone repair and reconstruction.*” (emphasis added)). Therefore, the Examiner has not shown that there would be a suggestion and/or a motivation to combine the teachings of these two references.

Even if assuming *arguendo* that one of skill in the art would have combined the teachings of these two patents, there would have been no reasonable expectation of success in achieving the claimed invention. As shown above, Jefferies does not disclose the complexed acidic phospholipid now claimed and Hollinger does not provide the missing information that would lead to the present claims. Furthermore, Hollinger leads a person of skill in the art to the contrary conclusion, *i.e.*, that materials such as collagen are immunogenic and should be avoided. This is opposite to the present claims. Thus, one of skill in the art would not reasonably expect to achieve the presently claimed invention by combining the teachings of these two references.

Since the Examiner has failed to prove any of the three criteria for proving *prima facie* obviousness of claims 27-28 and 31 over Jefferies in view of Hollinger, these claims are not obvious and the rejection should be withdrawn.

The Examiner also contends that claim 26<sup>2</sup> is obvious in view of Jefferies in further view of the prior art cited in the application at page 3, lines 10-23, which teach the utility of acidic phospholipids complex. This rejection is respectfully traversed.

As stated above, Jefferies does not disclose or suggest a complexed-acidic-phospholipid-collagen complex comprising calcium, phospholipids, inorganic phosphate, and collagen. The listed references merely discuss acidic phospholipids in general, their structure and ability to bind to collagen. They do not provide for the limitations of claim 26 that are not disclosed in Jefferies, *e.g.*, using a composite of calcium, phospholipid, inorganic phosphate, and collagen to promote calcifying tissue growth.

Because the references cited on page 3 of the application only discuss complexed-acidic-phospholipid-collagen in general, there would have been no reasonable expectation of success in achieving the claimed invention. The combination of teachings would not provide enough guidance to a person of skill in the art, especially given the fact that Jefferies does not disclose or suggest the claimed acidic phospholipids collagen complex. Thus, claim 26 is not obvious.

The Examiner also contends that claim 33 which covers a dosage of between 5 mg and about 5 g of the complexed-acidic-phospholipid-collagen would be obvious in view of the teachings of Jefferies alone. This rejection is respectfully traversed.

As fully discussed above, Jefferies does not disclose the method of claim 24 for inducing the growth of bone by applying an effective growth stimulating amount of a complexed-acidic-phospholipid-collagen composite, wherein the complex comprises calcium, phospholipids, inorganic phosphate, and collagen. Jefferies alone cannot suggest the amounts of complex to administer when Jefferies does not disclose or suggest the claimed complex to be administered. Moreover, there would be no motivation to modify Jefferies to obtain the claimed dosages because there is no teaching of the composite to be administered. Additionally, because there is no disclosure or suggestion of the

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<sup>2</sup> Claim 26 has been cancelled in this amendment. However, since the specific limitation of claim 26 has been added to claim 24, the arguments for non-obviousness of this claim are still relevant.



specifically claimed complex, it would not be routine for a person of skill in the art to determine the amount of composite to be administered from Jefferies and a person of skill in the art would not have a reasonable expectation of success in achieving the claimed invention based upon the disclosure of Jefferies alone. Thus, claim 33 is not obvious.

It is also respectfully submitted that the Examiner should consider objective evidence of unexpected results and advantages of the presently claimed invention over the prior art compositions for osteoinduction. *See In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998). These include lack of rejection of implant material, consistent bone growth across the region in need of growth without the disadvantages of rapid degradation of the composite material, cost-effectiveness, greater osteoinduction than collagen alone and/or in combination of non-stable peptides, and the lack of denaturation during standard sterilization procedures. See application, page 6, lines 27- page 7, line 2 and page 14, line 28- page 5, line 10. It should be noted that the first listed advantage, the lack of rejection, is especially surprising in view of the teachings of Hollinger regarding the unwanted immune response of natural materials, such as collagen.

For all of the above reasons, claims 26, 27, 28, 31, and 33 are not obvious.

It is duly noted that claims 14 and 34 appear to be free of any prior art.

**CONCLUSION**

In view of the above amendments and remarks, it is respectfully submitted that the pending claims are now in condition for allowance and such action is earnestly solicited. If the Examiner believes that a telephone conversation would help advance the prosecution in this case, the Examiner is respectfully requested to call the undersigned attorney at (212) 527-7631. The Examiner is hereby authorized to charge any additional fees associated with this response to our Deposit Account No. 04-0100.

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Respectfully submitted,

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